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BRUSCA, J EXAMINER

ART UNIT	PAPER NUMBER
1805	28

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This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☑ This application has been examined ☑ Responsive to communication filed on 5/26/94 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), — days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☑ Notice of References Cited by Examiner, PTO-892. (a.)
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____

Part II SUMMARY OF ACTION

1. ☑ Claims 1, 3-19 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☑ Claims 2 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☑ Claims 1, 3-19 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

EXAMINER'S ACTION

PTOL-326 (Rev. 2/93)

Part III DETAILED ACTION

1. The group and or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit 1805.

2. Applicant's arguments filed 5/26/94 have been fully considered but they are not deemed to be persuasive.

Specification

3. The incorporation of essential material by reference to a foreign application or foreign patent or to a publication inserted in the specification is improper. Applicant is required to amend the disclosure to include the material incorporated by reference. The amendment must be accompanied by an affidavit or declaration executed by the applicant, or applicant's attorney or agent, stating that the amendatory material consists of the same material incorporated by reference in the referencing application. *In re Hawkins*, 486 F.2d 569, 179 USPQ 157; *In re Hawkins*, 486 F.2d 579, 179 USPQ 163; *In re Hawkins*, 486 F.2d 577, 179 USPQ 167.

The applicant's attempt to amend the disclosure to include the material incorporated by reference filed 5/26/94 is not proper because no declaration accompanied the amendment. The proposed amendments to the specification will not be entered.

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The specification is objected to under 35 U.S.C. § 112, first paragraph, as the specification fails to adequately teach how to make and or use the invention.

In *Ex parte Forman*, 230 USPQ 546 (Bd. App. 1986), the Board considered the issue of enablement in molecular biology. The Board summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims. The Board also stated that although the level of skill in molecular biology is high, results of experiments in molecular biology are unpredictable.

In considering these factors for the instant claims:

(a) The steps of the method require:

1. isolation or synthesis of the target RNA molecule

2. determining the sequence of the target RNA molecule and the site in the RNA that is critical to function

3. determining the secondary and three-dimensional structure of the targeted site in the RNA molecule, in particular determining the structure flanking the critical site

4. synthesizing a compound that will bind specifically to the critical site within the minor groove of the target RNA molecule and thereby inhibit the function of the RNA molecule.

5. demonstrating that the synthesized compound can be used therapeutically to inhibit the function of the target RNA molecule in living cells.

(b) The amount of direction or guidance presented in the specification is limited to citations and discussions of prior art. The application does not distinctly describe procedures to perform any of the steps of the method. In particular, there is little guidance with regard to steps 3 -5 listed above. No guidance is given for the therapeutic use of a compound produced by the method of the invention.

(c) Although 8 working examples are presented, they are not drawn to the claimed method because the examples fail to demonstrate all steps of the method. No example is given of the design or the existence of a compound that inhibits the function of a target RNA molecule by binding to its minor groove. No example is given of the therapeutic use of a compound produced by the method of the invention.

(d) The nature of the invention is the design of compounds with therapeutic utility which inhibit the function of an RNA molecule by binding to its minor groove. The design of the RNA molecule is aided by analysis of the three-dimensional structure of the RNA molecule and by mutational analysis to determine sites critical to function.

(e) The prior art has characterized the structure of a number of RNA molecules successfully, and characterized a number of RNA-protein interactions in detail (including the determination of critical sites), but relatively little progress has been made towards generating compounds that specifically interact with critical sites on RNA molecules, and the Applicant has failed to point to any. A survey of the prior art does not reveal examples of drugs that inhibit RNA molecules by binding to their minor groove. Tuberactinomycin is a potent antibiotic that Yamada and Wank teach binds to RNA and can inhibit protein translation and splicing of group I introns. Tuberactinomycin binds to individual nucleotides in RNA molecules but has not been shown to bind to the minor groove of an RNA molecule. The references cited by the applicant on Page 43 as dealing with small molecules that bind to nucleic acids (Rebek et al., 1987; Jeong and Rebek, 1988; and Askew et al., 1989) discuss the interaction of synthetic molecules with purines and pyrimidines rather than nucleic acids. Wilson, et al., published three years after the filing date of the parent application, summarize the field of designing molecules that bind RNA as follows:

> It is interesting that no classes of small molecules have been defined that bind strongly in the minor groove of RNA or in the major groove of either RNA or DNA. The question of what types of small molecules bind in the grooves of RNA is extremely important for the design of RNA interactive drugs. There are no outstanding paradigms at this point to suggest design directions for RNA groove-binding drugs.

(f) The level of skill of those in the art of nucleic acid structure is high.

(g) It is not predictable which nucleotides are critical for function in an RNA molecule. For example, the specification teaches the unpredictability of the effect of introducing an amber anticodon into a tRNA molecule on Page 15. The unpredictability of mutated amber suppressor tRNAs when used in the "transplantation assay" is discussed on Pages 15-17.

(h) The claims are broadly drawn, encompassing many different modes of analysis of any RNA molecule.

The skilled practitioner would initially turn to the specification for guidelines for producing and using compounds that inhibit the function of RNA molecules. However, as set forth above, the specification does not provide guidance sufficient to practice the invention as claimed. As such, the practitioner would be required to turn to the prior art. However, as set forth above, a search of the prior art would have revealed neither methods for producing inhibitory compounds that bind to the minor groove of RNA molecules nor examples of such compounds. As such, the practitioner would have been forced to turn to empirical trial and error experimentation to attempt to produce inhibitory compounds of therapeutic utility that bind to the minor groove of RNA molecules. Said trial and error experimentation is the antithesis of enablement as defined under 35 USC 112, 1st paragragh and represents undue and excessive experimentation.

Claim Objections

5. Claims 1, and 3-19 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the objection to the specification.

6. Claims 1 - 10 and 14 - 16 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1, 3, 6-10, and 14-16 are indefinite for failing to provide positive process steps which clearly relate to the preamble. The preamble recites "A method for designing compounds specifically inhibiting targeted ribonucleic acid function" while the final method step is one of "synthesizing compounds that will bind specifically to the critical site within the minor groove of the targeted ribonucleic acid". It is suggested that the claim be amended to recite a correlation between the method steps and "inhibiting targeted ribonucleic acid function".

Claim 4 is indefinite for recitation of the phrase "compounds that inhibit protein synthesis from the targeted ribonucleic acid". It is not clear if the claim is limited to mRNA or merely RNA molecules that have a role in protein synthesis.

Claims 4 and 5 are indefinite because the term "protein synthesis" lacks antecedent basis.

Claim 5 is indefinite for not describing all members of the group as cells. It is suggested that the claim be amended by substitution of the phrase "bacterial cells" for "bacteria".

Claim 7 is indefinite for recitation of the phrase "analysis of the amino acid sequence derived from the mutated RNA". It is not clear what is meant by the phrase or how it relates to determination of the critical site.

Claims 9-10 are indefinite because the term "inhibitory compound" lacks antecedent basis.

Claims 10 and 13 are indefinite for recitation of the phrase "the carrier is selected from the group consisting of retroviral vectors". It is not clear how a retroviral vector can serve as a pharmaceutical carrier.

7. The rejection of claims 1, and 3-19 under 35 USC 103 is withdrawn.

8. Certain papers related to this application may be submitted to Art Unit 1805 by facsimile transmission. The FAX number is (703) 308-4312. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 CFR 1.6 (d)). NOTE: If applicant *does* submit a paper by FAX, the original copy should be retained

by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED, so as to avoid the processing of duplicate papers in the Office.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to John S. Brusca, Ph.D. whose telephone number is (703) 308-4231. The examiner can normally be reached on Monday through Friday from 9 AM to 5 PM. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mindy Fleisher, Ph.D., can be reached at (703) 308-0407.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

John S. Brusca, Ph.D.

Examiner

Mindy Fleisher

MINDY FLEISHER
SUPERVISORY PATENT EXAMINER
GROUP 1800